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ORIGINAL ARTICLE

Serum albumin and hospitalization among pediatric patients with end-stage renal disease who started dialysis therapy

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Abstract

Background Hypoalbuminemia is a strong predictor of hospitalization and mortality among adult dialysis patients. However, data are scant on the association between serum albumin and hospitalization among children new to dialysis.

Methods In a retrospective cohort study of children 1–17 years old with end-stage renal disease receiving dialysis therapy in a large US dialysis organization 2007–2011, we examined the association of serum albumin with hospitalization frequency and total hospitalization days using a negative binomial regression model.

Results Among 416 eligible patients, median (interquartile range) age was 14 (10–16) years and mean ± SD baseline serum albumin level was 3.7 ± 0.8 g/dL. Two hundred sixty-six patients (64%) were hospitalized during follow-up with an incidence rate of 2.2 (95%CI, 1.9–2.4) admissions per patient-year. There was a U-shaped association between serum albumin and hospitalization frequency; hospitalization rates (95%CI) were 2.7 (2.2–3.2), 1.9 (1.5–2.4), 1.6 (1.3–1.9), and 2.7 (1.7–3.6) per patient-year among patients with serum albumin levels < 3.5, 3.5– < 4.0, 4.0– < 4.5, and ≥ 4.5 g/dL, respectively. Case mix-adjusted hospitalization incidence rate ratios (IRRs) (95%CI) were 1.63 (1.24–2.13), 1.32 (1.10–1.58), and 1.25 (1.06–1.49) at serum albumin levels 3.0, 3.5, and 4.5 g/dL, respectively (reference: 4.0 g/dL). Similar trends were observed in hospitalization days. These associations remained robust against further adjustment for laboratory variables associated with malnutrition and inflammation.

Conclusions Both high and low serum albumin were associated with higher hospitalization in children starting dialysis. Because the observed association is novel and not fully explainable especially for high serum albumin levels, interpreting the results requires caution and further studies are needed to confirm and elucidate this association before clinical recommendations are made.

Keywords Hypoalbuminemia · Hyperalbuminemia · Hospitalization · Protein energy wasting · Incident dialysis patients

Introduction

Serum albumin is a strong predictor for adverse outcomes in adults with chronic kidney disease (CKD) [1]. Hypoalbuminemia may reflect poor nutrition, inflammation, or other systemic conditions associated with comorbidities [2]. Protein energy wasting (PEW) is common in patients with CKD and associated with adverse clinical outcomes [3]. PEW is closely associated with malnutrition and inflammation, where serum albumin is an established surrogate biomarker [4]. Children with CKD are also at high risk of poor nutrition and chronic inflammation [5, 6]. Because these conditions are amenable to treatments, recognition of hypoalbuminemia and underlying status may improve patient management, potentially leading to better clinical outcomes [7].

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Malnutrition and inflammation are associated with adverse outcomes such as death or hospitalization [8, 9]. Furthermore, among children with CKD, inadequate nutrition is one of the most common causes of growth failure, resulting in short stature or low body mass index (BMI) [10], which is also associated with death or hospitalization [11–14]. Hypoalbuminemia is known to be an independent predictor of survival and hospitalization in adult patients with end-stage renal disease (ESRD) on dialysis [15, 16]. In children with ESRD, a few studies have focused on mortality or hospitalization as outcomes, showing the association of hypoalbuminemia with high mortality in incident dialysis patients [17] and high hospitalization frequency in prevalent dialysis patients [18]. However, there are scarce data among pediatric patients new to dialysis therapy for the association between serum albumin and hospitalization. In addition, because previous studies have placed a particular emphasis on hypoalbuminemia as a marker of PEW, they estimated the association using two or three albumin categories without consideration of all levels of serum albumin. Thus, whether there is a non-linear association of serum albumin with hospitalization in pediatric dialysis patients is still unclear.

Therefore, we aimed to evaluate the association between serum albumin and hospitalization over a wide range of serum albumin levels among pediatric patients new to dialysis. We also examined the cross-sectional association of serum albumin with height and BMI.

Methods

Information on death, hospitalization, race/ethnicity, insurance, primary cause of ESRD, dialysis modality, comorbidities, medication, anthropometric data, and laboratory data was obtained from a statistically de-identified data set derived from the electronic database of the dialysis provider.

Patients

We retrospectively examined statistically de-identified data from all incident hemodialysis (HD) and peritoneal dialysis (PD) patients who were 1 to 17 years old and underwent dialysis treatment in facilities operated by a large dialysis organization in the USA from January 1, 2007 to December 31, 2011. We excluded patients with missing serum albumin data within 1 year from dialysis initiation, or were censored on the same date of the index albumin measurement. Patients were observed from the date of the first albumin measurement to transplantation, lost to follow-up, discontinuation of dialysis, or the end of follow-up (December 31, 2011), whichever occurred first.

Demographic, clinical, and laboratory measures

Comorbidities were defined based on International Classification of Diseases-9 (ICD-9) codes. Hypertension as a comorbidity was also applied for patients having systolic blood pressure ≥ 95th percentile at baseline [19].

Blood samples were drawn at the time of the clinic visit in PD patients and before dialysis session in HD patients using standardized techniques in all dialysis clinics and assayed typically within 24 hours of collection. All laboratory values were measured by automated and standardized methods in the central laboratory (Deland, FL). Serum albumin was measured centrally using the bromocresol green method. To minimize measurement variability, all repeated measures except serum albumin were averaged for each patient during each 91 days from dialysis initiation (i.e., patient-quarter), and the quarterly means in each quarter were used in all analyses. The first available serum albumin value after initiation of dialysis served as baseline, while the quarterly averaged values during the patient-quarter with the first available serum albumin draw served as baseline for the other laboratory data. Most laboratory values such as albumin, calcium, phosphorus, creatinine, and bicarbonate were measured monthly. Ferritin and intact parathyroid hormone (iPTH) were measured at least quarterly. Hemoglobin was measured weekly to biweekly in most patients.

Hospitalization records

We excluded hospitalization records with a date of admission prior to the index albumin measurement or after the censoring date. We also excluded records with admission and discharge on the same date, i.e., hospitalization was defined as a hospital admission that included at least one overnight stay. Hospitalizations likely related to kidney transplantation, which were defined as any hospitalization including the date of kidney transplantation, were also excluded. Previous discharge and next admission on the same date were considered as two distinct hospitalizations. For calculating hospitalization days, the admission day was counted as one full hospitalization day while the discharge day was not; one overnight stay in hospital was regarded as a hospitalization for 1 day.

Height and BMI

We used data on height extracted in the same year as the index albumin date and data on quarterly averaged body weight obtained from the same patient-quarter as the first available serum albumin. BMI was calculated using height and weight. Height and BMI values were age and sex standardized to z scores using the 2000 Centers for Disease Control and Prevention (CDC) Growth Chart.

Statistical analysis

Baseline characteristics are summarized with categorized serum albumin level as < 3.5 g/dL, 3.5 to < 4.0 g/dL, 4.0 to < 4.5 g/dL, and ≥ 4.5 g/dL, and are expressed as numbers (proportions), mean ± SD, or medians (interquartile range, IQR), as appropriate.

We used a negative binomial regression model to evaluate the associations of baseline serum albumin with hospitalization frequency and total hospitalization days because of overdispersion in the distribution of hospitalization frequency and days. We examined the cause-specific hospitalization as well as overall hospitalization in the hospitalization frequency analysis. As sensitivity analyses, baseline and time-dependent Cox regression models were used for time to first hospitalization. Since serum albumin levels may change within 1 year from dialysis initiation, and may influence the association between baseline serum albumin and hospitalization, we also examined the association between serum albumin and hospitalization frequency among patients with baseline serum albumin obtained within 3 months of dialysis initiation as a sensitivity analysis. Linear regression analysis was used to estimate the association of serum albumin with *z* scores of height and BMI. Results from negative binomial, Cox, and linear regression models were expressed as incidence rate ratios (IRRs), hazard ratios, and *z* score differences, respectively (reference serum albumin 4.0 g/dL). Baseline and time-varying serum albumin were also modeled as a continuous variable, and their associations with outcomes were estimated using restricted cubic spline functions with four knots [20].

Each model, except analyses for height and BMI, was examined with four levels of adjustment, i.e., unadjusted, case mix-adjusted, case mix plus height-adjusted, and a fully adjusted model which includes laboratory variables associated with malnutrition and inflammation. Unadjusted models consisted of baseline or time-varying albumin values. Case mix-adjusted models included serum albumin values plus age, sex, race/ethnicity (Caucasian, African American, Hispanic, other races), primary insurance (Medicare, Medicaid, other insurance), primary cause of ESRD (congenital anomalies of the kidney and urinary tract, glomerulonephritis, other cause), dialysis type (HD, PD), access type (central venous catheter, arteriovenous fistula [AVF], PD catheter), dialysis vintage, transplantation prior to first dialysis date, comorbidities (hypertension, cardiovascular disease, diabetes mellitus, endocrine/metabolic disease, autoimmune disease), and medication. For the case mix plus height-adjusted model, height *z* score was added to covariates in the case mix model. In fully adjusted models, we adjusted for all of the covariates in the case mix model plus height, BMI, baseline or time-varying hemoglobin, ferritin, iron saturation, albumin-corrected calcium, phosphorus, iPTH, white blood cell count, bicarbonate, and creatinine. We limited covariates to age, sex, and race/ethnicity when analyzing the associations with height and BMI.

We examined potential modification of the association between baseline serum albumin and hospitalization frequency by case mix variables, i.e., age, sex, race (African American or non-African American), dialysis type (HD or PD), and cause of ESRD (glomerulonephritis or not) by including each set of their interaction terms with spline functions of baseline serum albumin into regression models. Furthermore, we included all interaction terms into regression models and used stepwise backward selection for the interaction terms while retaining all the other covariates. Because dialysis modality and cause of ESRD are particularly important potential confounders and/or effect modifiers of the association between serum albumin and hospitalization, we performed subgroup analyses by dialysis modality (HD or PD) and cause of ESRD (glomerulonephritis or not). In addition, we focused on patients 1–< 6 years old and performed subgroup analysis by age (< 6 or ≥ 6 years) because younger patients may have lower serum albumin and high risk for hospitalization. We further conducted subgroup analyses based on the results of the interaction tests.

The frequency of missing data was less than 10% in most baseline variables, except for BMI (28%), and a multiple imputation method with 30 data sets was used for analyses. Missing laboratory values in time-dependent analysis including serum albumin were imputed with last observation carried forward. There were 40 missing values on serum albumin over a total of 965 patient-quarters. Analyses were performed using STATA MP, version 13.1 (Stata Corp, College Station, TX).

Results

Baseline characteristics

A total of 480 patients who initiated dialysis between 2007 and 2011 were identified. After excluding 4 patients who were censored on the same date as the index albumin measurement and 60 patients who had missing serum albumin data within 1 year from dialysis initiation, the final cohort comprised 416 pediatric dialysis patients (Fig. 1). In the final cohort, mean ± SD baseline albumin level was 3.7 ± 0.8 g/dL, median (IQR) dialysis vintage was 14 (6–40) days, and median (IQR) age was 14 (10–16) years old. Patients with lower serum albumin levels had lower levels of hemoglobin and serum creatinine (Table 1).

Hospitalization frequency, total hospitalization days, and time to first hospitalization

Among 416 included patients, 266 patients were hospitalized at least once within the observation period. The overall hospitalization rate and hospitalization days were 2.2 (95%CI,

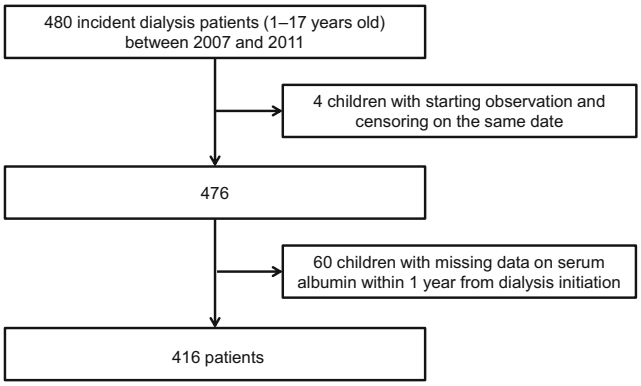

Fig. 1 Cohort construction

1.9–2.4) and 12.7 (95%CI, 10.3–15.0) days per patient-year, respectively. Patients with both lower and higher serum albumin appeared to have higher hospitalization rates and longer hospitalization days (Table 2). Consistently, the IRRs were higher for both lower and higher serum albumin, whereas the lowest risk was observed in the ranges of serum albumin levels 3.9–4.2 g/dL in the unadjusted, case mix-adjusted, case mix plus height adjusted, and fully adjusted models (Figs. 2 and 3). In the case mix-adjusted model, IRRs for hospitalization frequency were 1.63 (95%CI, 1.24–2.13), 1.32 (95%CI, 1.10–1.58), and 1.25 (95%CI, 1.06–1.49) at serum albumin levels of 3.0 g/dL, 3.5 g/dL, and 4.5 g/dL, respectively (reference: 4.0 g/dL). Likewise, adjusted IRRs for total hospitalization days were 2.06 (95%CI, 1.33–3.19), 1.48 (95%CI, 1.11–1.99), and 1.39 (95%CI, 1.06–1.83) at 3.0 g/dL, 3.5 g/dL, and 4.5 g/dL, respectively. The leading causes of hospitalization were infection (171 hospitalizations, 16%) and dialysis access-related hospitalization (73 hospitalizations, 7%) among a total of 1037 hospitalizations. In the case mix-adjusted model for hospitalization frequency, IRRs for infection-related hospitalization were 1.37 (95%CI, 0.79–2.37), 1.34 (95%CI, 0.93–1.95), and 0.83 (95%CI, 0.55–1.26); those for access-related hospitalization were 1.21 (95%CI, 0.58–2.52), 1.07 (95%CI, 0.66–1.74), and 1.32 (95%CI, 0.87–2.00) at serum albumin levels of 3.0 g/dL, 3.5 g/dL, and 4.5 g/dL, respectively (reference: 4.0 g/dL) (Supplemental Fig. 1). The association between serum albumin and hospitalization frequency was consistent in the restricted cohort of patients with baseline serum albumin obtained within 3 months of dialysis initiation (Supplemental Fig. 2). In the sensitivity analysis using time to the first hospitalization as the outcome, both baseline and time-dependent Cox models showed consistent associations (Fig. 4, Supplemental Fig. 3, Supplemental Table 1).

Subgroup analysis for hospitalization frequency

In subgroup analyses by age, dialysis modality, and cause of ESRD, the association between serum albumin and hospitalization frequency was consistent with the overall analysis in all of the subgroups (Supplemental Fig. 4–6).

Sex and race were potential effect modifiers on the associations between serum albumin and hospitalization frequency in the model including the respective interaction term with serum albumin on top of case mix variables, as well as in the backward stepwise selection models including all interaction terms of interest ($P_{\text{interaction}} < 0.2$ for both). Whereas males showed an association consistent with the overall analysis, there was no significant association with hospitalization frequency over the observed range of serum albumin levels among females (Fig. 5a, b). We further stratified sex and race into 4 groups, i.e., African American male, African American female, non-African American male, and non-African American female. The associations observed in male and female subgroups were consistent among non-African American patients (Fig. 5c, d). We did not estimate the association of serum albumin and hospitalization for African American male and female groups due to the small sample size.

Height and BMI

The analytical cohort for height included 401 patients with available data. Mean ± SD z score was -0.8 ± 1.5 and 81 patients (20%) were short stature, defined as a height less than −2.0 SD [21]. Both lower and higher albumin levels were associated with lower z score in the linear regression model (Fig. 6a). BMI data were available in 299 patients, and mean ± SD z score was 0.2 ± 1.4. Although BMI z score slightly decreased with higher albumin level, there was no significant difference according to serum albumin level overall (Fig. 6b).

Discussion

In this study of pediatric dialysis patients, baseline serum albumin levels showed a U-shaped association with hospitalization outcomes. A consistent association was observed in the time-varying model. The association of serum albumin with hospitalization frequency was modified by sex and race, and the hospitalization risk associated with low and/or high serum albumin was drastically attenuated in female patients. Serum albumin also showed a U-shaped association with height z score, while there was no particular relationship between serum albumin and BMI.

A U-shaped association between serum albumin and hospitalization was consistent across all adjustment levels for hospitalization frequency, total hospitalization days, and time to first hospitalization using both baseline and time-varying

Table 1 Baseline characteristics by serum albumin levels

	Total	Baseline serum albumin level (g/dL)			
		< 3.5	3.5 to < 4.0	4.0 to < 4.5	≥ 4.5
N (%)	416	130 (31)	108 (26)	121 (29)	57 (14)
Age (years)	14 (10–16)	13 (4–16)	15 (12–16)	15 (12–17)	14 (8–16)
< 6 years (%)	76 (18)	39 (30)	13 (12)	12 (10)	12 (21)
6 to < 13 years (%)	73 (18)	24 (18)	18 (17)	22 (18)	≤ 10
≥ 13 years (%)	267 (64)	67 (52)	77 (71)	87 (72)	36 (63)
Male (%)	225 (54)	71 (55)	47 (44)	71 (59)	36 (63)
Race/ethnicity (%)					
Caucasian	160 (38)	53 (41)	36 (33)	48 (40)	23 (40)
African American	95 (23)	31 (24)	28 (26)	25 (21)	11 (19)
Hispanic	130 (31)	34 (26)	35 (32)	40 (33)	21 (37)
Other	31 (7)	12 (9)	≤ 10	≤ 10	≤ 10
Insurance (%)					
Medicare	73 (18)	24 (18)	18 (17)	24 (20)	≤ 10
Medicaid	93 (22)	25 (19)	26 (24)	26 (21)	16 (28)
Other	250 (60)	81 (62)	64 (59)	71 (59)	34 (60)
Cause of ESRD (%)					
CAKUT	95 (23)	25 (19)	23 (21)	33 (27)	14 (25)
Glomerulonephritis	133 (32)	57 (44)	33 (31)	34 (28)	≤ 10
Other	188 (45)	48 (37)	52 (48)	54 (45)	34 (60)
Dialysis type (%)					
HD	232 (56)	64 (49)	68 (63)	71 (59)	29 (51)
PD	184 (44)	66 (51)	40 (37)	50 (41)	28 (49)
Access type (%)					
CV catheter	208 (50)	63 (48)	61 (56)	57 (47)	27 (47)
AVF	24 (6)	≤ 10	≤ 10	14 (12)	≤ 10
PD catheter	184 (44)	66 (51)	40 (37)	50 (41)	28 (49)
Dialysis vintage (days)	14 (6–40)	13 (4–28)	12 (6–29)	19 (7–59)	18 (7–42)
Height *z* score	− 0.8 ± 1.5	− 0.9 ± 1.5	− 0.6 ± 1.5	− 0.7 ± 1.3	− 1.1 ± 1.6
BMI *z* score	0.2 ± 1.4	0.3 ± 1.3	0.3 ± 1.4	0.2 ± 1.4	0.0 ± 1.3
Hemoglobin (g/dL)	11.1 ± 1.5	10.7 ± 1.5	11.1 ± 1.5	11.2 ± 1.3	11.5 ± 1.6
Ferritin (ng/mL)	196 (99–397)	184 (110–377)	222 (83–453)	162 (93–322)	245 (118–491)
Iron saturation (%)	28 ± 13	27 ± 11	28 ± 14	30 ± 15	27 ± 12
TIBC (μg/dL)	238 ± 55	213 ± 63	244 ± 50	250 ± 41	262 ± 48
Calcium (mg/dL)	9.4 ± 0.7	9.4 ± 0.8	9.3 ± 0.6	9.3 ± 0.7	9.7 ± 0.7
Phosphorus (mg/dL)	5.3 ± 1.3	5.3 ± 1.5	5.3 ± 1.2	5.3 ± 1.2	5.2 ± 1.3
iPTH (pg/mL)	305 (174–576)	286 (166–461)	349 (176–604)	315 (185–671)	280 (159–516)
Bicarbonate (mEq/L)	23.8 ± 3.2	24.0 ± 3.1	23.6 ± 3.1	23.6 ± 3.4	24.1 ± 2.9
Creatinine (mg/dL)	6.9 ± 3.5	5.9 ± 3.2	7.4 ± 3.3	7.4 ± 3.5	7.6 ± 4.1
White blood cell ($\times 10^3/mm^3$)	8.0 ± 3.2	8.6 ± 3.5	8.0 ± 3.2	7.2 ± 2.7	8.1 ± 3.6

Values for categorical variables are given as numbers and percentages; values for continuous variables, as mean ± standard deviation or median (interquartile range). Any cells with $N \leq 10$ are denoted as such due to patient confidentiality

SI conversion factors: to convert albumin to g/L, multiply by 10; hemoglobin to g/L, multiply by 10; ferritin to pmol/L, multiply by 2.247; TIBC to μmol/L, multiply by 0.179; calcium to mmol/L, multiply by 0.25; phosphorus to mmol/L, multiply by 0.323; iPTH to ng/L, multiply by 1.0; bicarbonate to mmol/L, multiply by 1.0; creatinine to μmol/L multiply by 88.4; white blood cell to $\times 10^9$ /L, multiply by 10^6

ESRD, end-stage renal disease; *CAKUT*, congenital anomalies of the kidney and urinary tract; *HD*, hemodialysis; *PD*, peritoneal dialysis; *CV*, central venous; *AVF*, arteriovenous fistula; *BMI*, body mass index; *TIBC*, total iron binding capacity; *iPTH*, intact parathyroid hormone

Table 2 Hospitalization frequency and total hospitalization days across serum albumin level

	Serum albumin level (g/dL)			
	< 3.5	3.5 to < 4.0	4.0 to < 4.5	≥ 4.5
Hospitalization frequency	2.7 (2.2–3.2)	1.9 (1.5–2.4)	1.6 (1.3–1.9)	2.7 (1.7–3.6)
Hospitalization days	15.1 (11.2–19.0)	13.0 (7.0–18.9)	8.1 (5.9–10.2)	17.1 (8.7–25.5)

Values are given as incidence rate (95%CI) per patient-year

serum albumin. The hospitalization risk incrementally decreased in the range of serum albumin levels between 3.0 and 4.0 g/dL. Considering the high prevalence of mild-to-moderate hypoalbuminemia in dialysis patients, the incremental risk for hospitalization in this range should be emphasized. Our results of increasing risk for hospitalization with hypoalbuminemia are consistent with previous studies in both children and adults [16–18, 22]. In regards to high albumin levels, some studies have showed a lower hospitalization risk with higher serum albumin levels over the wide range exceeding 4.0 g/dL [22], while another study showed the hospitalization risk leveling off in the range of > 4.0 g/dL [23]. Contrary to these reports, the risk remained beyond 4.0 g/dL in the present study. In the previous studies for children on maintenance dialysis, although some focused on serum albumin with hospitalization or mortality using a relatively large dialysis cohort, the association of higher serum albumin with these outcomes is still unclear because high albumin levels have tended to be regarded as normal albumin, and are usually categorized within the normal albumin group [17, 18]. In our study, we used cubic spline functions, which allowed us to evaluate the potential non-linear association with hospitalization over serum albumin levels extending into the high-normal range [24] and observed a U-shaped association. In terms of sex difference, a higher hospitalization frequency for female versus male patients has been reported in adults with ESRD [25].

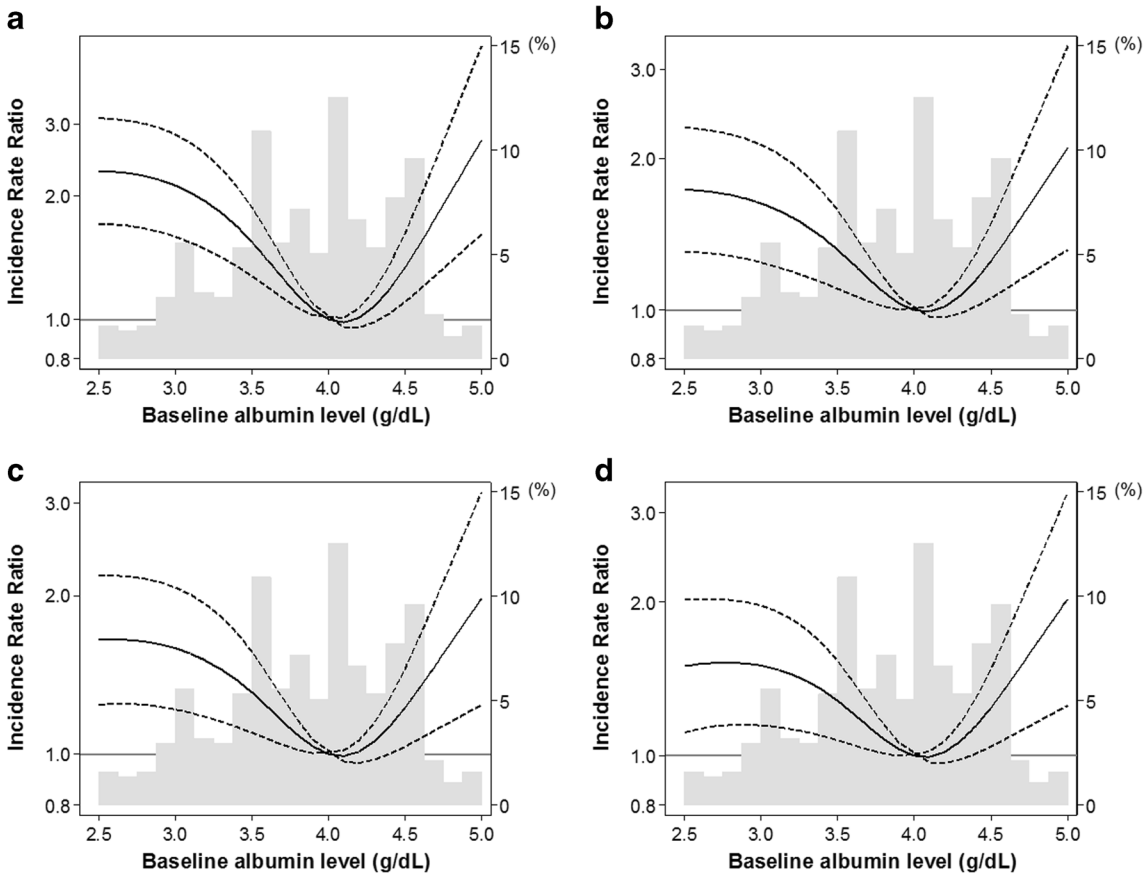

Fig. 2 Incidence rate ratios for hospitalization frequency with restricted cubic spline in **a** unadjusted, **b** case mix-adjusted, **c** case mix plus height-adjusted, and **d** fully adjusted models. Histogram is the distribution of baseline serum albumin level. Solid and dotted lines represent incidence rate ratio and 95% confidence interval, respectively. Incidence rate ratios were high in both lower and higher albumin levels for all models (reference: serum albumin 4.0 g/dL)

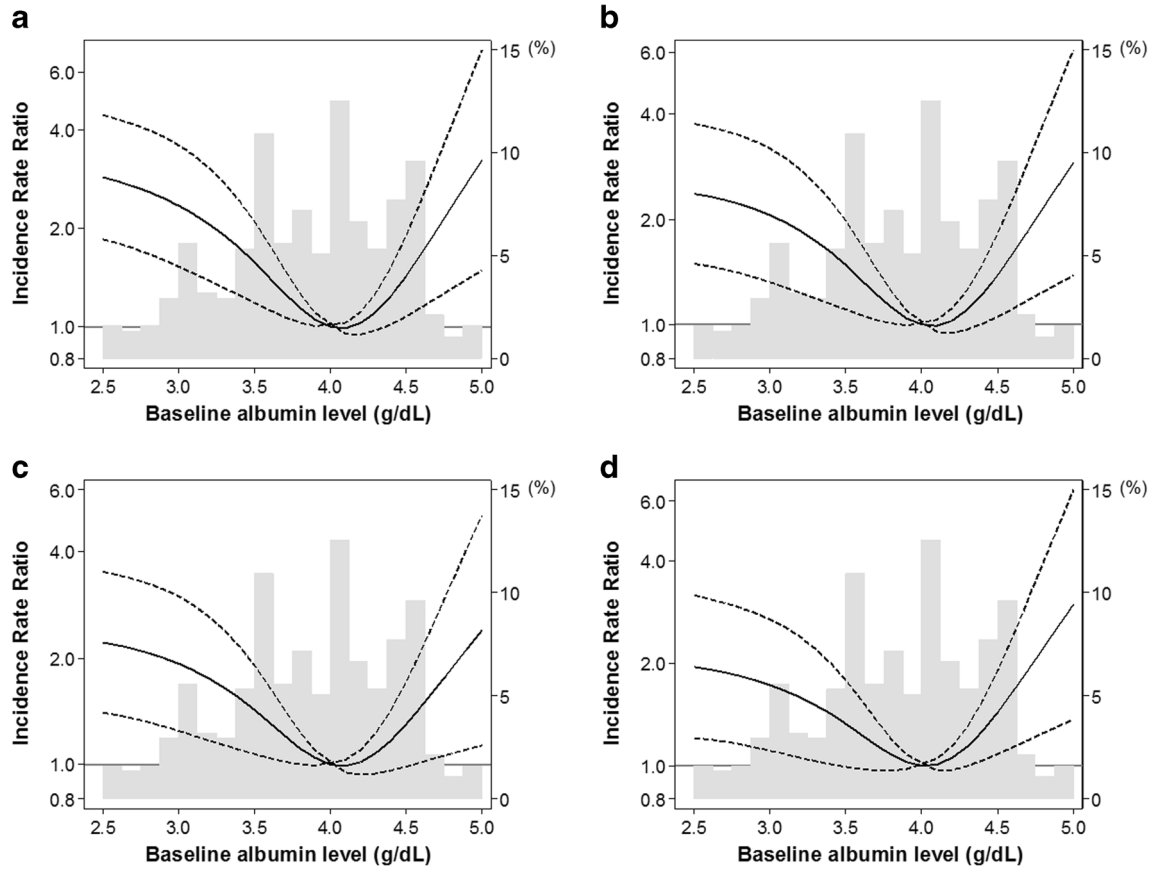

Fig. 3 Incidence rate ratios for total hospitalization days with restricted cubic spline in **a** unadjusted, **b** case mix-adjusted, **c** case mix plus height-adjusted, and **d** fully adjusted models. Histogram is the distribution of baseline serum albumin level. Solid and dotted lines represent incidence rate ratio and 95% confidence interval, respectively. Incidence rate ratios were high in both lower and higher albumin levels for all models (reference: serum albumin 4.0 g/dL)

However, there were no differences of either serum albumin or hospitalization frequency between male and female patients in our pediatric cohort. Instead, whereas low and high serum albumin were associated with high risk for hospitalization in males, the hospitalization risk did not change over the observed albumin level in females.

Inadequate growth, particularly short stature, should be taken into account when evaluating the presence and severity of PEW among children, in addition to those criteria used among adult patients, such as serum albumin and BMI [26]. Thus, hypoalbuminemia, short stature, and low BMI could all correlate with each other as manifestations of PEW among children. However, we found that baseline serum albumin was not associated with baseline BMI, although baseline serum albumin was weakly associated with baseline height. These parameters are not necessarily only for nutritional status but reflect various comorbid conditions which may induce inflammatory status and disturb the normal growth hormone axis [27, 28], and our results support this hypothesis.

Hypoalbuminemia is used as one of the criteria for PEW in patients with CKD [29], which is consistent with our findings in the present study. Some markers associated with nutrition and inflammation, such as hemoglobin and creatinine [30], had consistent trends with serum albumin levels at baseline. However, observed trends were not adjusted, i.e., important confounders such as age, height, and erythropoiesis-stimulating agent use were not taken into account. Moreover, other factors aside from PEW, such as fluid overload, may also underlie the association between hypoalbuminemia and high risk for hospitalization. Although accounting for fluid overload is challenging, the consistent association in the HD and PD groups might indicate less of an influence of fluid overload given that HD patients are more likely to have fluid overload compared with PD patients who often undergo blood draws after a full night of PD. Even if the effect of fluid overload is small, we should emphasize that hypoalbuminemia is not only a surrogate marker of PEW. Hypoalbuminemia and PEW have been the focus of attention among nephrologists, while high albumin has not been typically discussed. Although it remains unclear why we observed an increasing hospitalization risk with high albumin levels, high albumin may at least in part reflect unfavorable conditions resulting in dehydration, induced by difficulty

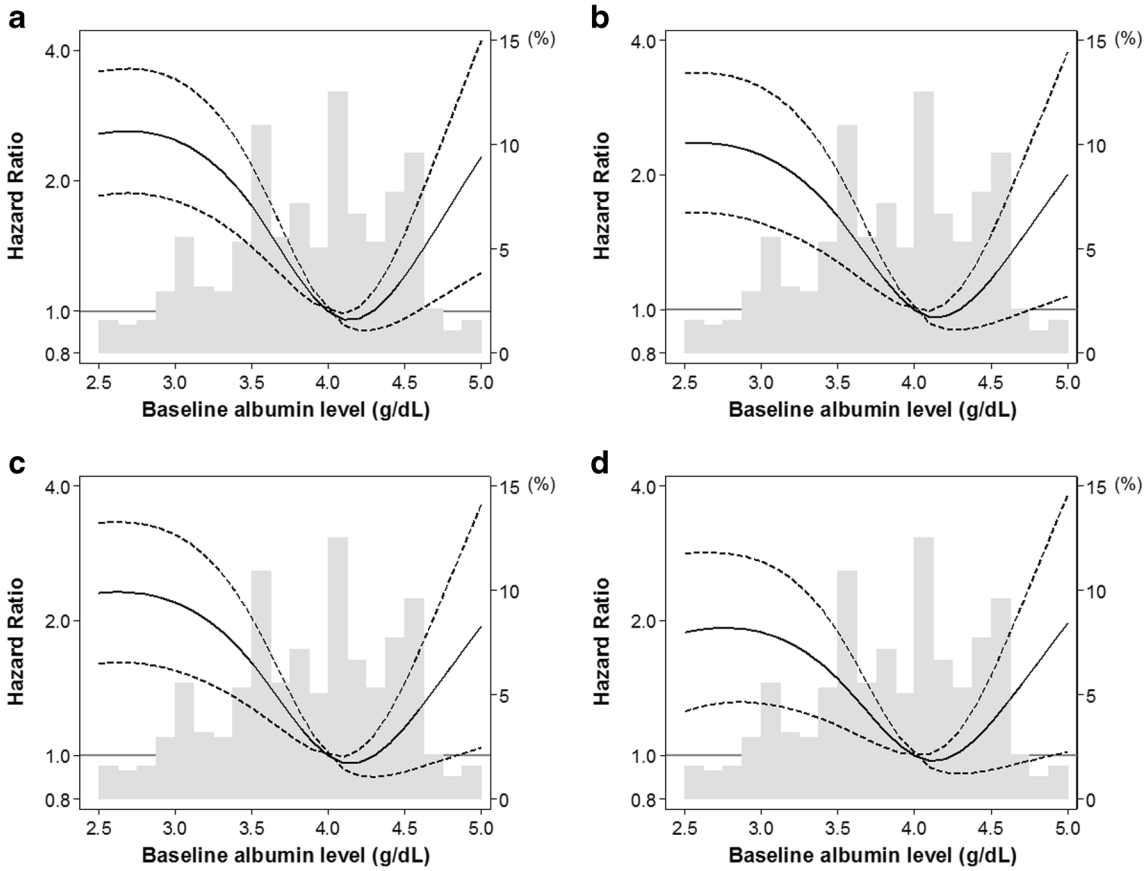

Fig. 4 Hazard ratios for first hospitalization with restricted cubic spline in **a** unadjusted, **b** case mix-adjusted, **c** case mix plus height-adjusted, and **d** fully adjusted models. Histogram is the distribution of baseline serum albumin level. Solid and dotted lines represent hazard ratio and 95% confidence interval, respectively. Hazard ratios were high in both lower and higher albumin levels for all models (reference: serum albumin 4.0 g/dL)

to estimate dry weight [31] or salt-losing kidney disease, such as seen in patients with a primary hypoplastic/dysplastic kidney leading to ESRD [32]. Hospitalization for high or normal serum albumin also may be due to a more favorable clinical status, such as the need for an AVF placement, which may require normal albumin and which results in hospitalization and operation after achievement of normal albumin. However, only 1% of total hospitalization counts included the date of AVF placement in our cohort, limiting our ability to evaluate this possibility. Our results for cause-specific hospitalization may imply that the risk for hospitalization associated with higher serum albumin could vary depending on the cause of hospitalization.

Several limitations should be acknowledged. First, due to the nature of an observational study, we could not make definitive statements about the causal associations of serum albumin level and hospitalization. We were also not able to exclude the possibility of the presence of unmeasured confounders and residual confounding, including unavailable or highly frequent missing data, such as dietary intake, normalized protein catabolic rate, and KT/V. We did not have information on active infection at baseline as well, which should be an exclusion criterion. Second, this study had limited statistical power due to small sample size. However, all of the associations between serum albumin and hospitalization were consistent, with relatively narrow 95% CIs. Third, we were unable to take into account urinary protein in the analyses due to absence of this information. Severe hypoalbuminemia may be largely attributed to heavy proteinuria rather than to PEW. The adjustment model including cause of ESRD and the subgroup analysis by glomerulonephritis and nonglomerulonephritis might be an indirect way to take into account urinary protein. Although the consistent U-shaped association in both subgroups might indicate less influence of urinary protein, we are not able to make any conclusions about the effect of urinary protein. Fourth, the results for cause-specific hospitalization might be less accurate because of small event numbers and frequently missing information. These limitations make it difficult to discuss the pathophysiology for our results. However, our findings

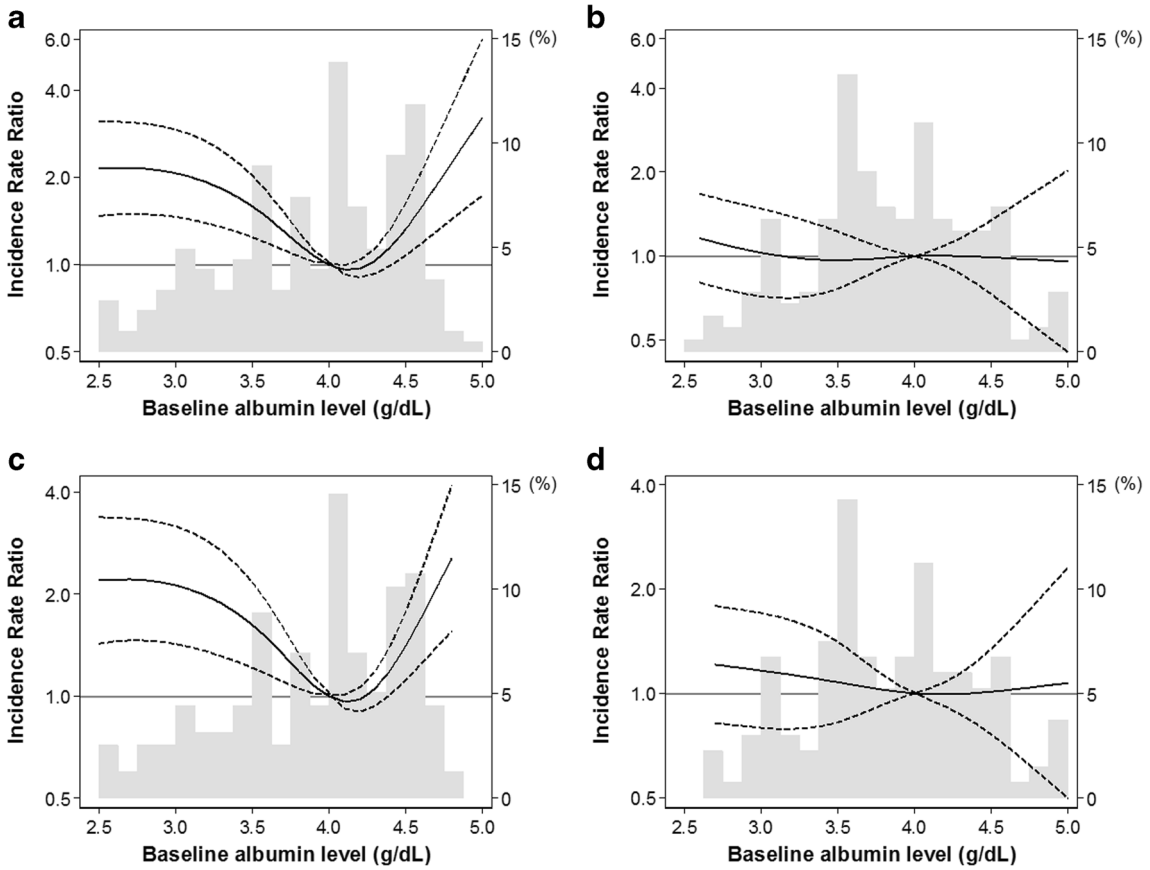

Fig. 5 Incidence rate ratios for hospitalization frequency with restricted cubic spline of **a** males and **b** females in case mix-adjusted model. Sex and races were further stratified into **c** non-African American male and **d** non-African American female. Histogram is the distribution of baseline serum albumin level. Solid and dotted lines represent incidence rate ratio and 95% confidence interval, respectively

strongly support the potential of serum albumin for the prediction and risk stratification of hospitalization among children with ESRD on dialysis.

In conclusion, serum albumin levels within 1 year of dialysis initiation showed a U-shaped association with hospitalization among children with ESRD on dialysis. Further studies are needed to confirm and elucidate the association between high serum albumin levels and hospitalization, as well as the gender difference in the albumin-hospitalization relationship among children.

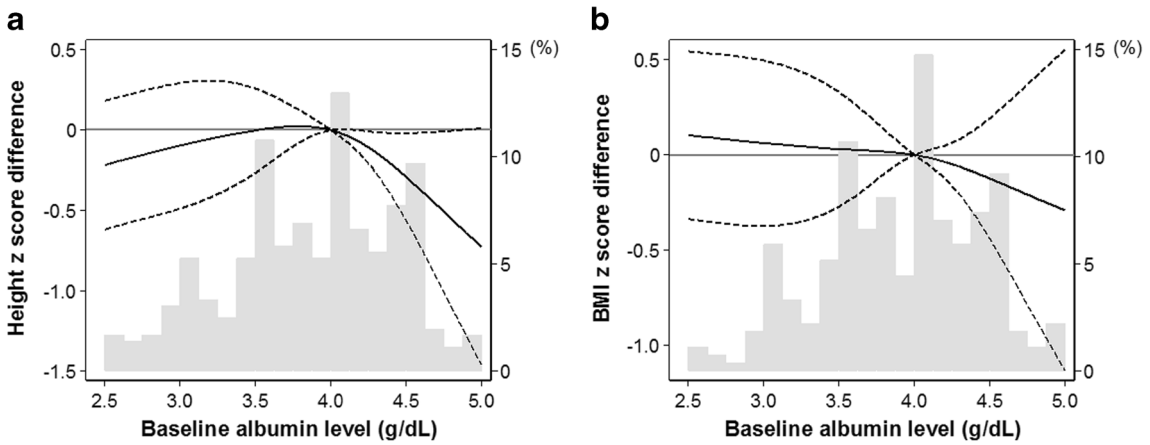

Fig. 6 **a** Height *z* score differences and **b** body mass index (BMI) *z* score differences in case mix-adjusted model. Histogram is the distribution of baseline serum albumin level. Solid and dotted lines represent z score difference and 95% confidence interval, respectively. Both lower and higher albumin levels were associated with lower height *z* score. BMI *z* score was slightly low in higher albumin level, whereas there was no difference in lower albumin level

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Compliance with ethical standards

This study was approved by the Institutional Review Boards of the Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles, University of California Irvine Medical Center, and the University of Washington as exempt from informed consent.

Conflict of interest K.K.-Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition and Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma.

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